

**The Influence of Cognitive Behavioral Therapy on Fatigue,
Cognition and Inflammatory Biomarkers in Multiple
Sclerosis Patients: Single Blinded Randomized Controlled
Trial**

RESULTS DATA ELEMENT

By

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الباحثة :- شيماء طه ، انجي بدرالدين صلاح

القسم:- العلوم الاساسية

عنوان البحث: -

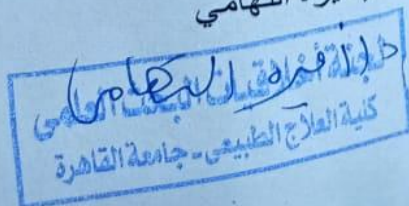
The efficacy of cognitive behavioural therapy on fatigue, cognition and inflammatory biomarkers in multiple sclerosis patients.

نحيطكم علما بموافقة لجنة أخلاقيات البحث العلمي علي خطة البحث المقدمة و تعتبر هذه الموافقة سارية اعتبارا من تاريخها.

و يرجي ملاحظة أنه يجب إخطار اللجنة علي الفور في حال وجود أي آثار سلبية غير متوقعة عليه قد تؤثر علي موافقة اللجنة.

رئيس لجنة أخلاقيات البحث العلمي

أ.د / اميره التهامي



RESULTS DATA ELEMENT

A total of 40 Remitting-Relapse MS patients with (Expanded Disability Status Scale<5) were divided into two groups, both groups are suffering cognitive decline (using RehaCom software to assess attention/concentration, memory and reaction behavior) with primary fatigue according to the Fatigue Severity Scale (FSS>36). Patients with depression and sleep problems were excluded from the study. Patients in both groups have elevated serum levels of tumor necrosis factor- α (TNF- α) and interferon- γ (IFN- γ).

The patients were assigned into two equal groups, Control group patients (GA) and Study group patients (GB) . Upper limb motor function was assessed using (FMA-UE) and hand grip dynamometer and Magstim Rapid2 system with a figure-of-eight coil was used to determine the level of cortical excitability (CAMT and IAMT) for both groups (GA and GB).

I. General chronological features of the patients in both groups:

Forty MS patients were recruited in this study with total mean and standard deviation of age (27.3 ± 3.982) years and total mean and standard deviation of duration of illness (4.4 ± 1.128) years. The mean values and standard deviation of age in (GA) were (27.45 ± 3.649) years and in (GB) were (27.15 ± 4.380) years respectively. Also, the mean values of duration of illness in (GA) were (4.35 ± 1.268) years and in (GB) were (4.45 ± 0.999) years respectively (fig.). Comparison of the mean values of age and duration of illness in (GA) and the corresponding variables in (GB) revealed no significant differences where the P-values in both groups were ($P \geq 0.05$). This means that the patient's age and duration of illness in both groups (G1 and G2) were statistically matched (table).

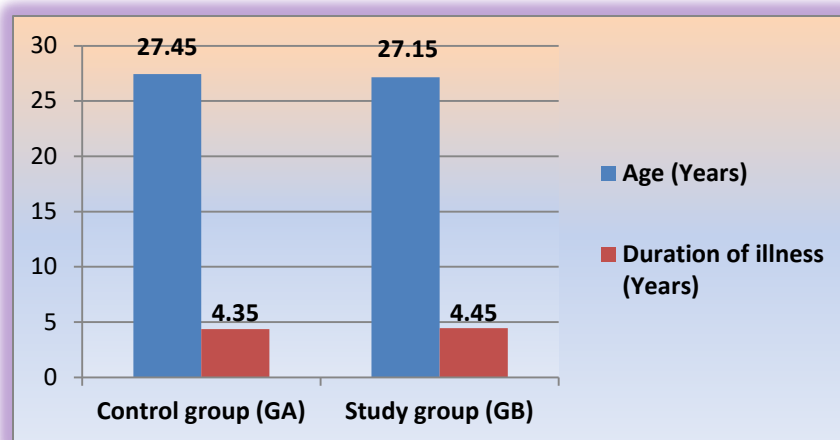


Fig (): Mean values of the Age and Duration of illness in both groups

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	p value	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Upper	Lower
Age (Years)	Equal variances assumed	1.313	0.259	0.235	38	0.815	0.300	1.275	-2.281	2.881
	Equal variances not assumed			0.235	36.798	0.815	0.300	1.275	-2.283	2.883
Duration of illness (years)	Equal variances assumed	2.781	0.104	-0.277	38	0.783	-0.100	0.361	-0.831	0.631
	Equal variances not assumed			-0.277	36.022	0.783	-0.100	0.361	-0.832	0.632

* p values ≤ 0.05 was considered statistically significant

Table (): Mean values of the Age and Duration of illness in both groups

II. General characteristics of the patients in both groups

(Gender & Smoking history)

a. Gender difference between GA and GB:

The **number of male patients** in (GA) was thirteen with a percent of 46.4% and in (GB) was fifteen with a percent of 53.6% of the total number within the male

patients .While, The **number of female patients** in (GA) was seven with a percent of 58.3 % and in (GB) was five with a percent of 41.7% of the total number within the female patients (Fig.). There was no significant difference between both groups in the percentage of male and female as p-value of the Pearson Chi-Square was (0.490). This means that the patient's gender and distribution in both groups (GA and GB) were statistically matched (table 4).

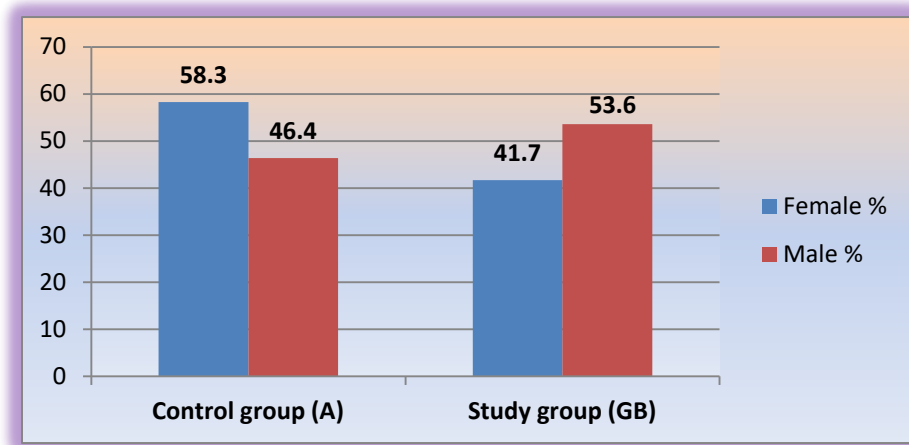


Fig (): Mean percentage of gender distribution in both groups

b. Smoking history difference between GA and GB:

The **number of Non-Smoking patients** in (GA) was ten with a percent of 43.5% and in (GB) was thirteen with a percent of 56.5% of the total number within the non-smoking patients .While, The **number of Smoking patients** in (GA) was ten with a percent of 58.8% and in (GB) was seven with a percent of 41.2% of the total number within the smoking patients (Fig.). There was no significant difference between both groups in the percentage of smoking history as p-value of the Pearson Chi-Square was (0.337). This means that the patient's smoking history and distribution in both groups (GA and GB) were statistically matched (table).

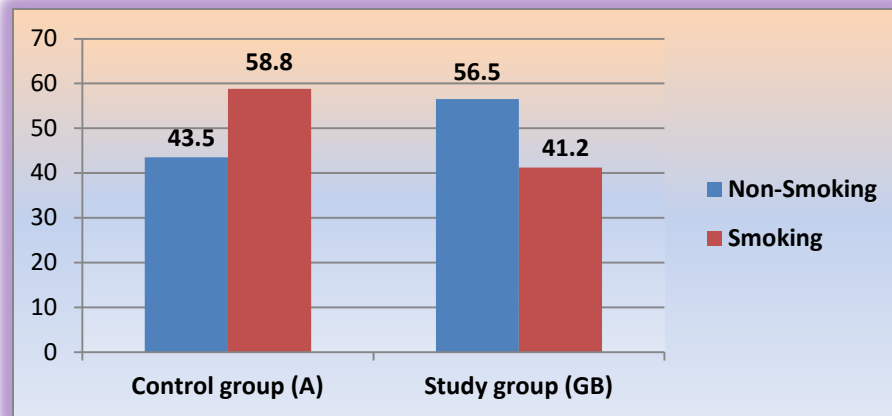


Fig (): Mean percentage of smoking history distribution in both groups

		Chi-Square Tests				
Main characteristics of patients		Value	df	p value	p value	p value
1. Gender difference	Pearson Chi-Square	.476(b)	1	0.490		
	Continuity Correction(a)	0.119	1	0.730		
	Likelihood Ratio	0.478	1	0.489		
	Fisher's Exact Test				0.731	0.366
	N of Valid Cases	40				
2. Smoking History		Value	df	p value	p value	p value
	Pearson Chi-Square	.921(b)	1	0.337		
	Continuity Correction(a)	0.409	1	0.522		
	Likelihood Ratio	0.925	1	0.336		
	Fisher's Exact Test				0.523	0.262
	N of Valid Cases	40				

* p values ≤ 0.05 was considered statistically significant

Table (): Percentage of Gender & smoking history distribution in both groups

III. The mean value of Expanded disability status scale (EDSS) scores in both groups:

The mean values of EDSS scores in (G1) and (G2) were (4.17±1.44), and (4.0±1.74) respectively. Comparison of the mean score of EDSS for both groups showed was no significant difference between both groups in the level of disability regarding the mean values of EDSS as p-value of the Pearson Chi-Square was (0.337). This means that the patient's EDSS in both groups (GA and GB) were statistically matched Where the t and P-values were (2.98, 0.3368) (table () and Fig ()).

Table (): Expanded disability status scale (EDSS) of control group (G1) and Study group (G2).

Patient groups	Expanded disability status scale scores (EDSS)		
	Mean	±SD	t-value
Control Group (G1)	4.17	±1.72	2.98
Study Group (G2)	4.0	±1.34	
			0.3368

SD: standard deviation, Significant: P* < 0.05

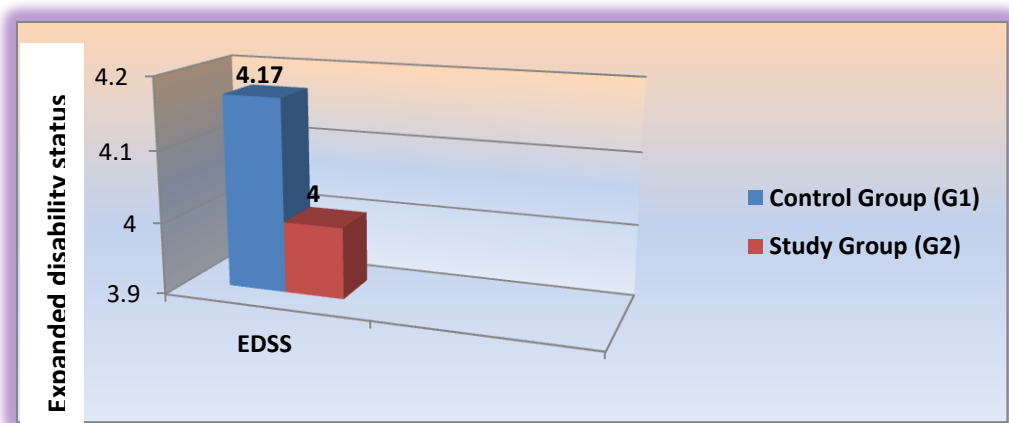


Fig.(): Mean value of the (EDSS) in both groups

IV. The Baseline mean values of Fatigue results in (G1) and (G2):

Table Fatigue severity scale results of control group (G1) and Study group (G2).

Patient groups	Fatigue Severity Scale (FSS)			
	Mean	±SD	t-value	P-value
Control Group (G1)	49.17	±1.72	2.98	0.3368
Study Group (G2)	51.22	±1.34		

SD: standard deviation, Significant: $P^* < 0.05$

V. The Baseline Rehacom Cognitive Baseline results in (G1) and (G2):

T test was used to compare the mean value and standard deviation of the Baseline Rehacom cognition results between both groups (G1 and G2) .

a- The Baseline mean values of Attention/Concentration (AC) test of Rehacom in both groups

The mean values of total score of Baseline maximum reaction time in (G1) and (G2) were **(42138.7 ± 5756.2ms)** and **(41388.9 ± 5460.8ms)** respectively. Comparison of the mean values of Baseline maximum reaction time in both groups using T test , revealed no significant difference between both groups in Baseline mean values of Attention/Concentration (AC) test, where the t and P-values were (3.29, 0.415) (table () and Fig ()).

(table 6,fig 26).

The mean values of total score of Baseline minimum reaction time in (G1)and (G2) were **(35273.4 ± 11257.4ms)**and **(32273.4 ± 11257.4ms)** respectively. Comparison of the mean values of Baseline minimum reaction time in both groups using T test , revealed no significant difference between both groups in Baseline mean values of Attention/Concentration (AC) test, where the t and P-values were (4.19, 0.365) (table () and Fig ()).

b. The Baseline mean values of Figural Memory (FM) test of Rehacom in both groups

The mean values of baseline total score of the percentage of correct responses in (G1) and (G2) were **(58.2± 6.94%)** and **(60.3± 8.04)** respectively .

Comparison of the mean values of Baseline percentage of correct responses in both groups using T test , revealed no significant difference between both groups in Baseline percentage of correct responses between both groups , where the t and P-values were (4.72, 0.246) (table () and Fig ()).

The mean values of baseline total score of the solution time in (G1) and (G2) were (**2424.8 ± 584.9 ms**) and (**2606.9± 594.9**) respectively. Comparison of the mean values of Baseline total score of the solution time in both groups using T test , revealed no significant difference between both groups in Baseline solution time between both groups , where the t and P-values were (3.371, 0.278) (table () and Fig ()).

c. The Baseline mean values of Reaction behavior (RB) test of Rehacom in both groups

The mean values of total Baseline score of the percentage of correct reactions in (G1) and (G2) were (**63.2± 6.14%**) and (**65.9± 6.82 %**) respectively . Comparison of the mean values of Baseline total score of the percentage of correct reactions in both groups using T test , revealed no significant difference between both groups in Baseline percentage of correct reactions between both groups , where the t and P-values were (4.371, 0.318) (table () and Fig ()).

The mean values of total score of the median reaction time in (G1) and (G2) were (**1664.8 ± 584.9 ms**) and (**1705.5 ± 601.2 ms**) respectively. Comparison of the mean values of Baseline total score of the median reaction time in both groups using T test , revealed no significant difference between both groups in Baseline median reaction time between both groups , where the t and P-values were (4.021, 0.288) (table () and Fig ()).

Table (6): Baseline Mean values of the different variables of attention/concentration and reaction behavior tests for (G1) and (G2) in Rehacom cognition testing.

Variable		Control group (G1)	Study group (G2)	T test	
		Mean \pm SD	Mean \pm SD	T value	P-value
Attention & Concentration	Maximum reaction time (ms)	42138.7 \pm 5756.2ms	41388.9 \pm 5460.8ms	3.29	0.415
	Minimum reaction time (ms)	35273.4 \pm 11257.4	32273.4 \pm 11257.4ms	4.19	0.365
Figural Memory	% of correct responses	58.2 \pm 6.94	60.3 \pm 8.04	4.72	0.246
	Solution Time (ms)	2424.9 \pm 584.9	2606.9 \pm 594.9	3.371	0.278

Reaction behavior	% of correct reactions	63.2± 6.14	65.9± 6.82	4.371	0.318
	Median reaction Time (ms)	1664.8 ± 584.9 ms	1705.5 ± 601.2 ms	4.021	0.288

SD: standard deviation,S:significant * : $P \leq 0.05$.

VI. The Baseline mean values of laboratory Proinflammatory cytokines in (G1) and (G2):

T test was used to compare the mean value and standard deviation of the proinflammatory cytokines laboratory results (TNF- α and IFN- γ) between both groups (G1 and G2).

The Baseline mean values of the total results of Tumor necrosis factor alpha (TNF- α) in (G1) and (G2) were **(88.58 \pm 15.94)** and **(89.52 \pm 16.11)** respectively . Comparison of the mean values of Baseline total results of Tumor necrosis factor alpha (TNF- α) in both groups using T test , revealed no significant difference between both groups in Baseline median reaction time between both groups , where the t and P-values were (3.021, 0.381) (table () and Fig ()).

The Baseline mean values of the total results of Interferon gamma (IFN- γ) in (G1) and (G2) were **(70.18 \pm 10.71)** and **(68.65 \pm 9.58)** respectively. Comparison of the mean values of Baseline total results of Interferon gamma (IFN- γ) in both groups using T test , revealed no significant difference between both groups in Baseline median reaction time between both groups , where the t and P-values were (3.018, 0.198) (table () and Fig ()).

Table (7): Mean values of the TNF- α and IFN- γ for (G1) and (G2) in proinflammatory cytokines blood level.

Variable		Control group (G1)	Study Group (G2)	F-value	P-value
		Mean \pm SD	Mean \pm SD		
Level of proinflammatory	TNF- α	88.58 \pm 15.94	89.52 \pm 16.11	3.021	0.381

cytokines	(pg/ml)				
	IFN- γ (pg/ml)	70.18\pm 10.71	68.65\pm 9.58	3.018	0.198

SD: standard deviation ,S:significant : P * \leq 0.05 .

VII. The Pre to Post treatment difference in the mean values of Fatigue results between both groups using Pairwise comparison (Bonferroni correction):

Comparison of the pre to post treatment difference between both groups revealed that level of fatigue was significantly decreased in G2 compared to G1 with (p value **0.0001**)

Table of Pre to post treatment difference Fatigue severity scale results between both groups

Variable	Pre-treatment				95% Confidence Interval		Post-treatment				95% Confidence Interval		F Value
	Mean± SD		MD	P			Mean± SD		MD	P			
	Control group	Study group			Lower Bound	Upper Bound	Control group	Study group			Lower Bound	Upper Bound	
Fatigue severity scale	47.5±2.94	48.1±2.46	-0.6	0.492*	-2.374	1.164	45.1±3.65	31.1±2.37	13.99	0.0001**	11.982	16.007	64.24

SD: standard deviation, Significant: P* < 0.05

VIII. The Pre to Post treatment difference in the mean values of the Rehacom Cognitive training results between both groups using Pairwise comparison (Bonferroni correction):

- Comparison of the pre to post treatment difference between both groups revealed that **Attention/Concentration** values of the Rehacom were significantly improved (both maximum and minimum reaction time significantly decreased in G2 compared to G1 with (p value **0.0001**))

Table of Pre to post treatment Attention/ Concentration results between both groups

Variable	Pre-treatment				95% Confidence Interval		Post-treatment				95% Confidence Interval		F Value
	Mean± SD		MD	P			Mean± SD		MD	P			
	Contr ol group	Study group			Low e r Boun d	Uppe r Boun d	Control group	Study group			Lower Bound	Upper Bound	
Maximum reaction time	4087 4.5 ±984 .55	40970. 1 ±1023. 39	- 95.6	0.768	 - 747. 083	 555. 87	39680. 35 ±1180. 91	2378. 63 ±2231 .1	1589 .71	0.0001*	14749.88	17049. 54	437.7
Minimum reaction time	352 52.0 5±3 51.5 2	35255 .57±3 57.58	-3.5	0.97 5	- 233. 62	226. 57	33647 .35±18 05.45	1838 7.1±2 60.07	1526 0.24	0.0001*	14412.213	16108. 27	1084. 7

SD: standard deviation, Significant: P* < 0.05

- Comparison of the pre to post treatment difference between both groups revealed that **Figural Memory** values of the Rehacom were significantly improved (Increased % of correct responses with decreased solution time in G2 compared to G1 with (p value **0.0001**)).

Table of Pre to post treatment Figural Memory results between both groups

Variable	Pre-treatment				95% Confidence Interval		Post-treatment				95% Confidence Interval		F Value
	Mean± SD		MD	P			Mean± SD		MD	P			
	Contr ol group	Stud y grou p			Low er Boun d	Upp er Bou nd	Control group	Study group			Lower Bound	Upper Bound	
% of correct response	54.35 ±2.58	54.21 ±2.39	0.13 9	0.798	- 1.47 8	1.75 7	59.45± 3.41	83.52 ±6.73	- 24.0 7	0.0001*	-27.414	-20.639	125.8
Solution time	2404. 3±68. 35	2397. 26±7 0.53	7.03	0.753	- 38.0 27	52.1 01	2236.2 5±78.6 1	935.4 2±26. 59	1300 .82	0.0001*	1262.331	1339.3 26	1482.9

SD: standard deviation, Significant: P* < 0.05

- Comparison of the pre to post treatment difference between both groups revealed that **Reaction Behavior** values of the Rehacom were significantly improved (Increased % of correct reactions with decreased median reaction in G2 compared to G1 with (p value **0.0001**)).

Table of Pre to post treatment Reaction Behavior results between both groups

Variable	Pre-treatment				95% Confidence Interval		Post-treatment				95% Confidence Interval		F Value
	Mean± SD		MD	P			Mean± SD		MD	P			
	Cont rol grou p	Study group			Low er Boun d	Upp er Bou nd	Control group	Study group			Lower Bound	Upper Bound	
% of correct reactions	60.95±3.79	62.21±3.64	-1.26	0.297	-3.675	1262.331	63.55±3.01	88.57±6.04	-25.02	0.0001*	-28.106	-21.952	125.5
Medium reaction time	1641.85±35.23	1638.47±38.97	3.37	0.778	-20.708	27.461	1563.3±51.53	829.31±13	733.98	0.0001*	709.298	758.67	1608.3

SD: standard deviation, Significant: P* < 0.05

IX. The Pre to Post treatment difference in the mean values of the laboratory Proinflammatory cytokines results between both groups

- Comparison of the **laboratory Proinflammatory cytokines (TNF- α and INF- γ)** pre to post treatment difference between both groups revealed that **laboratory Proinflammatory cytokines** were significantly improved in G2 compared to G1(there is significant decrease in the levels of both TNF- α and INF- γ in G2 compared to G1 with (p value **0.0001**)).

Table of Pre to post treatment Attention/ Concentration results between both groups

Variable	Pre-treatment				95% Confidence Interval		Post-treatment				95% Confidence Interval		F Value
	Mean± SD		MD	P			Mean± SD		MD	P			
	Contr ol group	Stud y grou p			Contro l group	Study group	Lower Bound	Upper Boun d			Lower Bound	Upper Bound	
TNF- α	82.6± 4.19	82.9 4±4. 7	-0.347	0.809	-3.238	2.543	77.1± 2.77	59.57± 3.37	17.52	0.0001*	15.523	19.519	73.08
IFN- γ	69.05 ± 1.87	69.8 9±1. 69	-0.845	0.574	-2.008	0.318	66.9± 3.27	52.57± 2.34	14.321	0.0001*	12.465	16.177	127.45

SD: standard deviation, Significant: P* < 0.05